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Abstract:

Pseudomonas aeruginosa is responsible for chronic infection in many bronchiectasis patients but it is not known whether it is associated with worse clinical outcomes independent of the underlying severity of disease.

This study analyzed data from 2596 bronchiectasis patients included from 10 different bronchiectasis clinical centres across Europe and Israel, with a 5-year follow-up period. Prevalence of *P. aeruginosa* chronic infection and its independent impact on exacerbations, hospitalizations, quality of life and mortality was assessed.

The prevalence of *P. aeruginosa* chronic infection was 15.0% (n=389). *P.aeruginosa* was associated with a higher mortality in a univariate analysis (HR: 2.02; 95% CI 1.53–2.66;p<0.0001) but an independent impact on mortality was not found in a multivariate analysis (HR: 0.98; 95% CI 0.70–1.36;p=0.89). *P. aeruginosa* was independently associated with increased mortality only in patients with frequent exacerbations (2 or more per year) (HR 2.03; 95% CI 1.36–3.03;p=0.001). An independent association with worse quality of life of 7.46 points (95% CI, 2.93-12.00; p=0.001) was found in a multivariable linear regression. *P. aeruginosa* was therefore found to be independently associated with exacerbation frequency, hospital admissions and worse quality of life. Mortality was increased in patients with *P. aeruginosa* particularly in the presence of frequent exacerbations.

Take home message:

Frequent exacerbations are the key determinants of long-term outcome in patients with *Pseudomonas aeruginosa* chronic infection.

Background:

Bronchiectasis is a chronic and progressive respiratory disease characterized by permanent dilation of bronchi, impairment of mucus clearance, chronic cough and sputum production, and an increased frequency of respiratory infections.(1) Without effective mucociliary and innate antimicrobial defences, there is a higher risk of chronic bacterial infection of the airways which can lead to an increase in airway inflammation and structural damage.(2,3)

Pseudomonas aeruginosa is one of the most important organisms causing chronic infection in bronchiectasis, because of its capacity to maintain virulence despite antibiotic therapies by forming biofilms and easily developing antimicrobial resistance.(4,5,6) *P. aeruginosa* in cystic fibrosis (CF) bronchiectasis is associated with a steeper decrease in lung function and increased morbidity and mortality.(7) Its presence in bronchiectasis seems to be linked with a more severe disease but whether there is a direct effect on disease progression or whether *P. aeruginosa* is just an indicator of existing clinical severity remains a topic of discussion.(8,9,10)

In a recent meta-analysis, *P. aeruginosa* chronic infection was related to a threefold increase in mortality, as well as a higher risk of hospital admissions and increased exacerbation frequency.(11) This study however, was not able to take into account the multiple confounders that are usually present in more severe bronchiectasis patients and that could play a role in mortality, such as FEV_1 , co-morbidities or severe exacerbations. Moreover, there was some heterogeneity in terms of chronic infection definition and measured parameters across the different studies.(11) To definitively answer whether *P. aeruginosa* directly drives disease progression and mortality in bronchiectasis would require a longitudinal study able to identify the point at which *P. aeruginosa* infection first occurs and to compare morbidity before and after acquisition. As such studies are not currently available, an alternative method is to utilise multivariable modelling, which allows the estimation of the independent contribution of *P. aeruginosa* after removing the effects of confounding variables.

The rate of *P. aeruginosa* chronic infection in bronchiectasis patients varies among the studies, between 9-31%, and its prevalence in a large, multicentre population from several different countries is yet to be assessed.(12-19)

The aim of this study was to assess the burden of disease in *P. aeruginosa* chronic infection and its independent impact in terms of patient outcomes.

Methods:

This study analyzed data from bronchiectasis patients enrolled in 10 different bronchiectasis clinical centres across Europe (including Israel as an EU affiliated country) (Dundee, Edinburgh, Newcastle–United Kingdom; Haifa-Israel; Galway-Ireland; Leuven-Belgium; Athens-Greece; Monza-Italy; Barcelona-Spain; Vojvodina-Serbia) between 2007 and 2013. Consecutive patients aged ≥18 years with a diagnosis of bronchiectasis, made by a specialist physician, based on high-resolution computed tomographic scan and with a compatible clinical history (defined by the presence of respiratory symptoms attributable to bronchiectasis) were enrolled. Patients had to be free from antibiotic treatment for exacerbation for 4 weeks prior to enrolment and initial data collection. Patients with CF or traction bronchiectasis due to pulmonary fibrosis were excluded, as well as patients with active non-tuberculous mycobacterial (NTM) disease. Local ethics committee or institutional review board, approved the data collection at each site.

Diagnostic work-up and assessment was made following algorithms consistent with the 2010 British Thoracic Society (BTS) guidelines.(20)

Identification of microorganisms and susceptibility testing were performed according to standard methods.(21) Chronic infection was defined by isolation of the same pathogen in two or more cultures, at least 3 months apart in a 12-month period.(20)

Demographics, previous medical history, comorbidities, as well as radiological, laboratory and microbiological findings were obtained from a combination of direct patient history, medical records and laboratory information recorded at each site. Quality of life (QoL) was measured by the St. George's Respiratory Questionnaire (SGRQ) and severity of disease was evaluated by the Bronchiectasis Severity Index (BSI).(22) There was a follow-up period of 5 years, in which exacerbations and hospitalizations were recorded, following BTS guidelines definitions, and mortality was assessed.

Statistical analysis:

Simple descriptive statistics of mean with standard deviation (SD) were used for continuous parametric data, median with 25-75% interquartile range (IQR) for continuous non-parametric data, and frequencies and percentages for categorical data. Subgroup comparisons were performed using the unpaired t-test, Mann-Witney U-Test or Chi-squared test, depending on data distribution.

Kaplan–Meier curves were used to illustrate survival data. For multivariable mortality analysis, Cox proportional hazard regression analysis was performed to estimate hazard ratios (HR) and their 95% confidence intervals (CI). Variables included in the model were those determined by the investigators to be clinically significant in impacting on mortality. In a sensitivity analysis, changes in prophylactic antibiotic therapy during the study were examined as a confounder in a Cox proportional hazard regression with treatment as a time varying covariate.

A multiple linear regression model was applied to determine the variables with an independent impact on QoL. To check the suitability of our model, we fitted a generalized linear model (GLM) with quasibinomial errors and a logit link. The signs and significance of every estimated parameter in this, matched its equivalent in the linear model. Estimates of the change in fitted values, from the GLM, on stepping one unit away from the centre of the dataset (the medians of all numerical values) in each direction all fell within the 95% CI around the betas in the linear model. However, while the model results are very similar, the terms within the generalized linear model are difficult to interpret. We have, therefore, described the results of the linear model.

All analyses were performed using SPSS version 21 (SPSS, Chicago, IL, USA) for Windows platform and Graph Pad Prism Version 5 (Graph Pad Software, Inc. San Diego, CA, USA).

Results:

Patient characteristics:

The study population was composed of 2596 patients. Individual inclusion per site was 608 in Edinburgh, 504 in Dundee, 116 in Newcastle, 280 in Galway, 190 in Leuven, 113 in Vojvodina, 88 in Haifa, 159 in Athens, 198 in Barcelona and 340 in Monza.

The patient characteristics are described in detail in table 1.

The median age was 67 years (IQR – 57-74) and there was a female predominance (61.1%, n=1586). In terms of comorbidities, the highest reported conditions were ischaemic heart disease, 17.5% (n=453), Chronic Obstructive Pulmonary Disease (COPD), 16.6% (n=431), GERD, 15.2% (n=394) and diabetes, 10.0% (n=260). The median BSI score was 6 (IQR – 4-10) with a homogenous distribution between the severity groups – Mild (0-4) (29.0%, n=753), Moderate (5-8) (35.7%, n=927), Severe (≥9) (35.3%, n=916). Patients had a median of 41.2 points in the SGRQ (IQR – 24.5 – 59.6). Most patients were classified as idiopathic (42%), with post-infective aetiology (17%), COPD (9%), asthma (6%), connective tissue diseases (6%) and allergic bronchopulmonary aspergillosis (5%) also being common in this cohort.

At the time of enrolment, the median number of exacerbations in the previous year was 2 (IQR – 0-3), however, 37.2% (n=966) had 3 or more exacerbations over the same period, and 25.9% (n=672) had at least one hospitalization in the previous year.

Pseudomonas aeruginosa chronic infection prevalence:

Half of the study population had a chronic respiratory infection with at least one pathogen (50.1%, n=1300). The most common were *Haemophilus influenzae* (21.9%, 95% CI 20.4-23.6%, n=569) and *P. aeruginosa (*15.0%, 95% CI 13.7-16.4%, n=389). Rates of *P. aeruginosa* infection varied across different European centres, from the lowest in Serbia - 0.9% (95% CI, 0.2-4.8%), Belgium - 8.4% (5.3-13.2%), Italy - 12.1% (9.0-15.9%), UK - 12.5% (10.7-14.4%) and Ireland - 13.9% (10.4-18.5%) to the highest rates in Spain - 21.2% (16.1-27.4%), Greece - 36.5% (29.4-44.2%) and Israel - 44.3% (34.4-54.7%). Active NTM was excluded, but NTM isolation as baseline was reported in 46 subjects.

Patient characteristics according to chronic infection status

Patients with *P.aeruginosa* were slightly older (median (IQR), 70y (59-77y) vs 67y (57-74y) vs 66y (57-75y), p<0.001) and had a lower FEV1% (57.9% vs 69.2% vs 77.0%, p<0.001) than patients chronically infected with other pathogens or those not chronically infected respectively.(table 3) They had more major cardiovascular comorbidities such as ischaemic heart disease and stroke. They had also more exacerbations on the previous year (median (IQR) – 3 (2-4) vs 2 (1-3) vs 1 (0-2), p<0.001) and a higher percentage of patients with at least one hospital admission in the previous year (59.9% vs 31.9% vs 17.6%, p<0.000). The median BSI was higher in *P. aeruginosa* group (median (IQR) – 13 (10-17) vs 8 (5-13) vs 5 (3-8), p<0.001). Data are presented in Table 2.

Mortality analysis:

There were 281 deaths during the follow-up period, which accounted for 10.8% (95% CI 9.7-12.1%) of the total study population. There were 73 deaths in 389 patients (18.8%) in the *P. aeruginosa* chronic infection group, 75 in 918 (8.2%) in the other pathogens chronic infection group and 133 in 1289 (10.3%) in patients with no chronic infection (p<0.0001 comparing all 3 groups).

A univariate analysis of the impact *P. aeruginosa* chronic infection had in terms of mortality, showed a higher mortality in the *P. aeruginosa* group versus all the other patients (HR: 2.02; 95% CI, 1.53–2.66; p<0.0001).(Figure 1)

A multivariate analysis was then performed with the variables that were determined to be clinically relevant affecting mortality.(Table 3) These results show that the presence of a *P. aeruginosa* chronic infection in isolation does not have an independent impact in terms of mortality (HR: 0.98; 95% CI 0.70 – 1.36; p=0.89). Other variables however, such as age (HR: 1.05; 95% CI 1.04-1.07; p<0.001), exacerbation frequency (HR (per exacerbation): 1.06; 95% CI 1.01 – 1.12; p=0.02) and hospitalized exacerbations (HR:1.60; 95% CI 1.17 – 2.19; p=0.003) had an independent contribution to a higher mortality.

We hypothesized that mortality associated with *P. aeruginosa* chronic infection may be exacerbation dependent. A separate analysis in terms of mortality was made dividing the study population into 4 categories – 1) *P. aeruginosa* chronic infection with less than 2 exacerbations per year; 2) *P. aeruginosa* chronic infection with 2 or more exacerbations per year; 3) No *P. aeruginosa* and less than 2 exacerbations per year; 4) No *P. aeruginosa* and 2 or more exacerbations per year.

Patients with *P. aeruginosa* and 2 or more exacerbations per year had the higher mortality rate (20.5%), followed by patients with frequent exacerbations without *P. aeruginosa* (12.5%). In those with less than 2 exacerbations per year, the mortality rate in the presence of *P. aeruginosa* chronic infection was 9.7% vs 6.7% in those without *P. aeruginosa* chronic infection. Of note, only 62 out of 389 patients with *P. aeruginosa* had less than 2 exacerbations per year.

Survival curves of the 4 groups are presented on figure 2.

A multivariate analysis was performed using the same variables (table 4). Having *P. aeruginosa* chronic infection with less than 2 exacerbations had no impact in terms of mortality (HR: 0.90; 95% CI 0.39 – 2.12; p=0.81). Patients having 2 or more exacerbations per year had increased mortality (HR: 1.74; 95% CI 1.28–2.38; p<0.001) an effect that was magnified in the presence of *P. aeruginosa* (HR: 2.03; 95% CI 1.36–3.03; p=0.001).

A sensitivity analysis accounting for centre as an independent variable in the analysis did not affect the conclusions (HR: 1.09, 95% CI 0.78-1.53;p=0.6) in the fully adjusted analysis. The same was observed in the analysis of subgroups by exacerbation history - *P. aeruginosa* plus a history of 2 exacerbations per year (HR: 2.22, 95% CI 1.44-3.43,p<0.0001), 2 or more exacerbations per year without *P. aeruginosa* (HR: 1.88, 95% CI 1.34-2.60,p<0.0001). *P. aeruginosa* without a history of frequent exacerbations was not associated with mortality (HR: 0.90, 95% CI 0.38-2.12,p=0.8). Finally, in a sensitivity analysis including changes in treatment during follow-up as a time varying co-variate, no difference in the conclusions were found. Hazard ratios were *P. aeruginosa* plus a history of 2 exacerbations per year (HR: 2.01, 95% CI 1.26-3.22,p=0.003), 2 or

more exacerbations per year without *P. aeruginosa* (HR: 1.80, 95% CI 1.27-2.55,p=0.001). *P. aeruginosa* without a history of frequent exacerbations was not associated with mortality (HR: 0.82, 95% CI 0.32-2.09,p=0.7). New antibiotic treatment (oral or inhaled) during follow-up was not significantly associated with mortality HR 0.78 95% CI 0.46-1.34,p=0.4.

Risk of exacerbations and hospital admissions:

P. aeruginosa as well as *H. influenzae* chronic infection constituted predictors of future exacerbations (Incident rate ratio (95% CI)) - 1.14 (1.04-1.27) and 1.13 (1.03-1.24) respectively.

Patients with *P. aeruginosa* chronic infection had a much higher probability of having a hospital admission on a univariate analysis (Odds ratio(OR): 4.96; 95% CI 3.96-6.22; p<0.001). This effect was also seen, although to a lesser degree, in a multivariable analysis (OR: 2.28; 95% CI 1.69-3.08; p<0.001).

Quality of life analysis:

The median value of SGRQ in the *P. aeruginosa* group was 58.1 points (IQR – 54.0 – 62.2) and was higher than the median values for the other pathogens and the no chronic infection groups. A multivariable linear regression was performed showing an independent increase in the SGRQ of 7.46 points (95% CI 2.93-12.00; p=0.001), higher than the minimal clinically important difference (MCID) for SGRQ which is 4 points.(23) These results were confirmed on the generalized linear model with quasibinomial errors and a logit link.

Discussion:

This is the largest single study of bronchiectasis patients with the aim to assess the prevalence and burden of *P. aeruginosa* chronic infection.

While multiple studies have reported an association between *P. aeruginosa* and more severe bronchiectasis, and some have shown an association with poorer clinical outcomes, these were predominantly single centre, with small samples sizes and could not provide any information as to whether *P. aeruginosa* was a cause of poor outcomes or simply a marker of more severe disease. Our study contributes to this debate by clearly demonstrating that after adjustment for multiple possible confounding variables, *P. aeruginosa* remains associated with increased exacerbations, increased hospital admission risk and worse quality of life. An association with mortality was only demonstrated in patients experiencing frequent exacerbations.

The prevalence of *P. aeruginosa* chronic infection in this study population was 15.0%, which is in keeping with the ranges of prior publications (9-31%).(12-18) In a recent meta-analysis, Finch et al. identified a rate of *P. aeruginosa* colonization of 24.1%, but the various studies included had different definitions of chronic colonization with some regarding a single isolate as indicative of chronic infection.(11) Mortality in this study population, with a follow-up of 5 years, was

10.8%, which is within the range of prior quoted studies over 4-5 years follow-up (Loebinger 9% at 4 years, Goeminne 20% at 5 years).(12, 24)

Several studies have identified *P. aeruginosa* chronic infection as a risk factor for mortality in bronchiectasis patients.(11, 12, 22, 24, 25) A pooled OR for mortality was 2.95 (95% CI 1.98–4.40; p<0.0001) in the Finch meta-analysis. In our cohort, on the univariate analysis, we had a HR of 2.02 (95% CI 1.53–2.66; p<0.0001). Because this group of patients has more risk factors than other groups, such as poorer lung function, increased age, certain comorbidities, it is important to clearly assess if *P. aeruginosa* really has an independent impact factor on mortality. In that matter, a multivariate analysis was performed. Herein independent predictors of mortality were age, low BMI, number of exacerbations, but in isolation, persistent infection with *P. aeruginosa* was not.

To better understand why there was such a difference between univariate and multivariate analysis, the study population was divided into 4 groups (in terms of *P. aeruginosa* chronic infection and number of exacerbations) and a new multivariate analysis was performed. It became clear that having exacerbations plays a major role in mortality, independent of *P. aeruginosa* status. This data strengthens the importance of reducing exacerbations in all bronchiectasis patients, particularly in the case of *P. aeruginosa* chronic infection, where a higher mortality risk is seen with frequent exacerbations.

Even allowing for varying thresholds for admission across different healthcare systems, where home intravenous antibiotic may/may not be available, *P. aeruginosa* appears strongly correlated with exacerbation frequency and the risk of hospitalization. The risk of hospital admission is related to severity of disease, number of exacerbations, and the antibiotic susceptibility pattern of the pathogen responsible for the exacerbation, which in the case of *P. aeruginosa* is often limited to IV antibiotics.

Quality of life was evaluated in this study using the SGRQ, which has been extensively validated in bronchiectasis patients.(26) *P. aeruginosa* chronic infection has been associated with a lower quality of life, and in the Finch et al. meta-analysis there was an 18.2 points decrement in the SGRQ.(11, 22, 27) The decrement justified by the presence of *P. aeruginosa* chronic infection was of 7.46 points (95% CI 2.93 – 12.00; p=0.001) which is considerably lower than the meta-analysis result. However, since it was adjusted for multiple variables, it gives us a better understanding of the real impact of this chronic infection in QoL, and it is still clearly clinically significant and far above the MCID for SGRQ.

If we accept now that there is robust evidence that *P. aeruginosa* drives worse outcomes in bronchiectasis there are a number of clinical implications. First, a limited amount of observational data suggest that it may be possible to prevent *P. aeruginosa* chronic infection by giving eradication treatment with oral, intravenous and/or inhaled antibiotics in combination.(28) A conditional recommendation in favour of this approach was provided in the 2017 ERS bronchiectasis guidelines.(29)Secondly, If *P. aeruginosa* infection cannot be prevented, then our data suggest that patients experiencing frequent exacerbations have the worst outcomes and so exacerbation prevention should be the key therapeutic focus. Long term macrolides have been shown to reduce exacerbation frequency in bronchiectasis, but these studies included few subjects with *P. aeruginosa*.(30) Inhaled antibiotics such as colistin, aminoglycosides and aztreonam have been tested in large populations of patients with *P. aeruginosa* with equivocal results.(29) Larger studies are awaited. The ERS bronchiectasis guidelines provided a conditional recommendation for the use of inhaled antibotics for patients

with *P. aeruginosa* and 3 or more exacerbations per year, with macrolides to be added if inhaled antibiotics fail to control exacerbations.(29) Our results reinforce the importance of following these recommendations alongside optimising airway clearance, vaccination and the use of pulmonary rehabilitation in these patients.(29)

The strengths of this study are the substantial number of patients included, the evaluation at different bronchiectasis clinical sites in different countries across Europe, and the considerable amount of patient data collected. A significant number of events, related to the large study population, enabled us to have a robust multivariate analysis with many variables, which helped to better understand the independent impact of *P. aeruginosa* chronic infection. Despite this, we acknowledge that the number of patients with *P. aeruginosa* not having frequent exacerbations was low. We cannot exclude the possibility that this group has an increased risk of death.

The main limitation of this study is not having a description of the cause of death in all cohorts. It would have been useful to know the number of deaths associated with respiratory causes. Another important limitation is that *P. aeruginosa* diagnosis is based on sputum culture which is known to be insensitive, and the methods and frequency of sputum culture are not standardized.(31) This could potentially underestimate the frequency of *P. aeruginosa* chronic infection. Another limitation is the absence of an analysis of the impact that *P. aeruginosa* phenotype/strain type and resistance pattern could have in terms of patient's outcomes.(31)

This study gives us a more accurate view of the real *P. aeruginosa* chronic infection prevalence across Europe. It also enables us to better understand its burden of disease, with connection to poorer lung function, more exacerbations and hospitalizations and a worse quality of life. In terms of mortality, the relationship between *P. aeruginosa* and an increased risk of death, described previously in the literature, seems to be closely related with the fact that these patients have more exacerbations and more hospitalizations, rather than just the simple fact of being chronically infected by this pathogen. Our analysis cannot fully account for the "chicken or egg" question of which characteristic comes first in disease. It is not known whether patients with *P. aeruginosa* have more exacerbations and therefore have worse outcomes, or whether frequently exacerbating patients have a poor prognosis with frequent antibiotic courses leading to *P. aeruginosa* infection and poor outcomes. Our study can only demonstrate that the combination of these two parameters leads to increase mortality. The mechanism by which exacerbations contribute to increase mortality in bronchiectasis is not fully understood and should be the subject of detailed translational research. Our work could have major implications for healthcare policy, it implies that adverse effects of *P. aeruginosa* may be mitigated by exacerbation prevention. Furthermore, it highlights the important impact of exacerbations in the non- *Pseudomonas* population validating this as a key therapeutic target.

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Total, n (%)	2596 (100%)
Demographics	
Age, yr, median, IQR	67 (57-74)
≥ 65 years old, n (%)	1395 (53.7%)
Male, n (%)	1010 (38.9%)
BMI, kg/m2, median (IQR)	24.8 (21.8-28.1)
Smokers and ex-smokers, n (%)	990 (38.1%)
Comorbidities	
Ischaemic heart disease, n (%)	453 (17.5%)
Stroke, n (%)	152 (5.9%)
Diabetes, n (%)	260 (10.0%)
Liver disease, n (%)	41 (1.6%)
Chronic renal failure, n (%)	154 (5.9%)
COPD, n (%)	431 (16.6%)
Asthma, n (%)	226 (8.7%)
Connective tissue disease, n (%)	210 (8.1%)
Neurological disease, n (%)	68 (2.6%)
Osteoporosis, n (%)	192 (7.4%)
GERD, n (%)	394 (15.2%)
Haematological malignancy, n (%)	33 (1.3%)
Solid tumor, n (%)	164 (6.3%)
Functional status	
FEV1 % predicted, median (IQR)	73.8% (54.0-92.1)
FEV1 % predicted, < 50%, n (%)	502 (19.3%)
Clinical status	
Exacerbations in the previous year, median (IQR)	2 (0-3)
3 or more exacerbations per year, n (%)	966 (37.2%)
At least one hospitalization in the previous year, n (%)	672 (25.9%)
Disease severity	
BSI score, median (IQR)	6 (4-10)
Mild BSI score (0–4), n (%)	753 (29.0%)
Moderate BSI score (5–8), n (%)	927 (35.7%)
Severe BSI score (>9), n (%)	916 (35.3%)
Quality of life	
SGRQ, median (IQR) n=987	41.2 (24.5-59.6)

Table 1 - Patient Characteristics. BMI – Body mass index; COPD – Chronic obstructive lung disease; GERD – Gastroesophageal reflux disease; IQR – Interquartile Range; BSI – Bronchiectasis Severity Index; SGRQ - St. George's Respiratory Questionnaire

	P. aeruginosa chronic infection	Other pathogen chronic infection	No chronic infection	p value
Total, n (%)	389 (15.0%)	918 (35.4%)	1289 (49.7%)	
Demographics				
Age, yr, median, IQR	70 (59-77)	67 (57-74)	66 (57-75)	p<0.001
≥ 65 years old, n (%)	244 (62.7%)	685 (74.6%)	674 (52.3%)	p<0.001
Male, n (%)	167 (42.9%)	522 (41.7%)	468 (36.3%)	p<0.001
BMI, kg/m2, median (IQR)	24.9 (21.3-27.7)	24.6 (21.4-27.7)	25.2 (22.3-28.4)	p<0.001
Smokers and ex-smokers, n (%)	122 (31.4%)	457 (49.8%)	516 (40.0%)	p<0.001
Comorbidities				
Ischaemic heart disease, n (%)	64 (16.5%)	251 (20.0%)	190 (14.7%)	p<0.001
Stroke, n (%)	30 (7.7%)	79 (6.3%)	69 (5.4%)	p=0.009
Diabetes, n (%)	53 (13.6%)	115 (9.2%)	137 (10.6%)	p=0.18
Chronic Renal Failure, n(%)	23 (5.9%)	61 (4.9%)	88 (6.8%)	p=0.82
COPD, n (%)	78 (20.1%)	196 (15.7%)	229 (17.8%)	p=0.10
Haematological malignancy, n (%)	9 (2.3%)	22 (1.8%)	11 (0.9%)	p=0.009
Solid tumor, n (%)	27 (6.9%)	88 (7.0%)	71 (5.5%)	p=0.001
Functional status				
FEV1 % predicted, median (IQR)	57.9 (42-77.7)	69.2 (50-89.8)	77.0 (59-95)	p<0.001
FEV1 % predicted, < 50%, n (%)	135 (34.7%)	290 (31.6%)	200 (15.5%)	p<0.001
Clinical status				
Exacerbations in the previous year, median (IQR)	3 (2-4)	2 (1-3)	1 (0-2)	p<0.001
At least one hospitalization in the previous year, n (%)	233 (59.9%)	400 (31.9%)	227 (17.6%)	p<0.001
Disease severity				
BSI score, median (IQR)	13 (10-17)	8 (5-13)	5 (3-8)	p<0.001
Mild BSI score (0–4), n (%)	0 (0%)	209 (22.8%)	543 (42.1%)	p<0.001
Moderate BSI score (5–8), n (%)	54 (13.9%)	461 (50.2%)	458 (35.5%)	p<0.001
Severe BSI score (>9), n (%)	335 (86.1%)	581 (63.3%)	288 (22.3%)	p<0.001
Quality of life				
SGRQ, median (IQR)	58.7 (42.0-79.3) n=125	44.5 (26.8-62.6) n=517	35.6 (21.0-52.3) n=345	p<0.001

Table 2 – Differences between patients with *P. aeruginosa* chronic infection, other pathogens chronic infection and no chronic infection

Variable	Hazard ratio for death	95% confidence interval	p value
P. aeruginosa chronic infection	0.98	0.70 – 1.36	0.89
Age (years)	1.05	1.04 - 1.07	<0.001
Gender (male vs female)	1.29	0.99 – 1.67	0.06
MRC dyspnea score	1.25	1.11 – 1.40	<0.001
FEV1 groups			
<30% predicted	1.00	n/a	reference
30-49% predicted	0.66	0.43 – 0.99	0.05
50-79% predicted	0.44	0.29 – 0.68	<0.001
80% or more predicted	0.45	0.28 – 0.73	0.001
Hospitalized exacerbations	1.60	1.17 – 2.19	0.003
Radiology score (Reiff Score)	1.02	0.99 – 1.06	0.17
BMI <18.5 Kg/m^2	1.70	1.14 – 2.54	0.01
Smoking status	1.14	0.86 – 1.50	0.37
Exacerbations in the previous year (HR per additional exacerbation)	1.06	1.01 – 1.12	0.02
H. influenzae chronic infection	0.59	0.40 – 0.86	0.007
S. aureus chronic infection	1.69	1.10 – 2.60	0.02
M. catarrhalis chronic infection	0.72	0.39 – 1.33	0.30
Enterobacteriaceae chronic infection	0.71	0.44 – 1.15	0.16
COPD	1.41	1.04 – 1.90	0.03
Diabetes	1.27	0.92 – 1.75	0.14
Chronic renal failure	1.46	1.03 – 2.06	0.03
Ischemic heart disease	1.47	1.12 - 1.93	0.006
Oral long term antibiotic suppressive therapy	1.11	0.84 – 1.47	0.46
Nebulized long term antibiotic suppressive therapy	0.80	0.51 – 1.25	0.33

Table 3 - Multivariate Cox regression analysis of factors associated with survival

Table 4 - Multivariate Cox regression analysis of factors associated with survival after categorization into 4 new groups

Variable	Hazard ratio for death	95% confidence interval	p value
Groups			
No *P. aeruginosa* chronic infection with <2 exacerbations per year	1.00	reference	n/a
No *P. aeruginosa* chronic infection with ≥2 exacerbations per year	1.74	1.28 – 2.38	<0.001
P. aeruginosa chronic infection with <2 exacerbations per year	0.90	0.39 – 2.12	0.81
P. aeruginosa chronic infection with ≥2 exacerbations per year	2.03	1.36 – 3.03	0.001
Age (years)	1.05	1.04 - 1.07	<0.001
Gender (male vs female)	1.29	1.00 – 1.68	0.055
Radiology score (Reiff Score)	1.03	0.99 – 1.06	0.11
BMI < 18.5 Kg/m^2	1.68	1.13 – 2.50	0.011
Smoking status	1.11	0.84 – 1.47	0.45
MRC dyspnea score	1.24	1.16 – 1.45	<0.001
FEV1 % predicted			
<30% predicted	1.00	Reference	n/a
30-49% predicted	0.66	0.44 – 1.00	0.048
50-79% predicted	0.41	0.27 – 0.62	<0.001
80% or more predicted	0.43	0.27 – 0.68	<0.001
H. influenzae chronic infection	0.57	0.39 – 0.84	0.005
S. aureus chronic infection	1.73	1.10 – 2.60	0.01
M. catarrhalis chronic infection	0.78	0.43 – 1.44	0.43
Enterobacteriaceae chronic infection	0.78	0.49 – 1.24	0.29
COPD	1.33	0.98 – 1.81	0.07
Diabetes	1.28	0.93 – 1.75	0.13
Chronic renal failure	1.58	1.13 – 2.23	0.008
Ischemic heart disease	1.46	1.11 - 1.92	0.007
Oral long term antibiotic suppressive therapy	1.14	0.86 – 1.49	0.36
Nebulized long term antibiotic suppressive therapy	0.79	0.51 – 1.25	0.32